



Predictive Value of the HAS-BLED and ATRIA Bleeding Scores for the Risk of Serious Bleeding in a “Real-World” Population With Atrial Fibrillation Receiving Anticoagulant Therapy

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Background: Despite the clear net clinical benefit of oral anticoagulation for stroke prevention in patients with atrial fibrillation (AF), the occurrence of major bleeding events may be devastating. The HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly) bleeding risk score was first described in 2010 and is recommended in European and Canadian guidelines to estimate major bleeding risk. In 2011, the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study group described a new bleeding risk scheme for AF, which includes five weighted risk factors: anemia, severe renal disease, age ≥ 75 years, previous hemorrhage, and diagnosed hypertension. We assessed the predictive value of the ATRIA bleeding score in a large cohort of patients with AF receiving anticoagulant therapy, compared with the well-validated HAS-BLED score.

Methods: We recruited consecutive patients with AF receiving anticoagulant therapy from our outpatient anticoagulation clinic with an INR between 2.0 and 3.0 during the previous 6 months' clinic visits. During follow-up, major bleeding events were assessed. We assessed both bleeding risk scores as quantitative variables or as dichotomized variables (low-moderate risk vs high risk). Model performance was evaluated by calculating C statistics, and the improvement in predictive accuracy was evaluated by calculating the net reclassification improvement (NRI) and the integrated discrimination improvement (IDI).

Results: We included 937 patients (49% men; median age, 76 years). Median (interquartile range) follow-up was 952 (785-1,074) days, during which 79 (8%) suffered a major bleeding event (annual rate, 3.2%). The HAS-BLED score had a model performance (based on C statistics) similar to that of the ATRIA score as a quantitative variable (C statistic, 0.71 vs 0.68; $P = .356$) but was superior to the ATRIA score when analyzed as a dichotomized variable (C statistic, 0.68 vs 0.59; $P = .035$). Both NRI and IDI analyses demonstrated that the HAS-BLED score more accurately predicted major bleeding episodes than did the ATRIA risk score, as reflected in the percentage of events reclassified correctly.

Conclusion: The HAS-BLED score shows significantly better prediction accuracy than the weighted (and more complex) ATRIA score. Our findings reinforce the incremental usefulness of the simple HAS-BLED score over other published bleeding risk scores in patients with AF receiving anticoagulant therapy.
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Abbreviations: AF = atrial fibrillation; ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; CHADS₂ = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and prior stroke or transient ischemic attack; CHA₂DS₂-VASc = cardiac failure or dysfunction, hypertension, age ≥ 75 years (doubled), diabetes, stroke (doubled), vascular disease, age 65-74 years, sex (female) category; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; HEMORR₂HAGES = hepatic or renal disease, ethanol use, malignancy, reduced platelet count, re-bleeding, hypertension, anemia, genetic factors, elevated risk of fall including neuropsychiatric disease, stroke; HR = hazard ratio; IDI = integrated discrimination improvement; INR = international normalized ratio; IQR = interquartile range; NRI = net reclassification improvement; OAC = oral anticoagulation

Oral anticoagulation (OAC) is highly effective in reducing the risk of stroke and mortality, compared with placebo/control in patients with atrial fibrillation (AF),¹ and the decision to give thromboprophylaxis has classically been based on stroke risk, as assessed by different stroke risk stratification schemes.² Despite the clear net clinical benefit of OAC in stroke prevention in patients with AF, the occurrence of major bleeding events may be devastating.³ The decision to use OAC should therefore be based on a careful assessment of both stroke risk and bleeding risk.

In contrast to stroke risk assessment schemes in AF, clinical scores for bleeding risk estimation in AF are less well established. Many risk factors for thromboembolism, such as advanced age, uncontrolled hypertension, history of ischemic heart disease, cerebrovascular disease, or previous bleeding events, have also been identified as risk factors for bleeding.⁴ Some factors that increase bleeding risk may be transient (or correctable), such as labile international normalized ratio (INR) values, invasive procedures, or drug/food interactions.

The HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly) bleeding risk score was first described in 2010 and is now recommended in the European and Canadian AF guidelines to estimate major bleeding risk in patients with AF receiving anticoagulant therapy.⁵⁻⁷ The HAS-BLED scheme has been validated in various European cohorts,⁷⁻¹⁰ as well as in an AF trial cohort receiving anticoagulant therapy.¹¹

In 2011, the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study group described a new bleeding risk scheme for AF, which includes five weighted risk factors (anemia, severe renal disease, age \geq 75 years, previous hemorrhage, and diagnosed

hypertension)¹² reporting a C statistic of 0.74 and performing well against older bleeding risk scores, although there was no comparison made against the HAS-BLED score. The aim of our study was to assess the clinical usefulness of the new ATRIA bleeding score in a large cohort of stable, patients with AF receiving anticoagulant therapy, compared with the well-validated HAS-BLED score.

MATERIALS AND METHODS

We studied consecutive patients with permanent or paroxysmal AF from our outpatient anticoagulation clinic database, who were initially seen from March to November 2007. To homogenize the cohort of patients and to avoid potential confounding factors (such as INR instability), only patients who had an INR between 2.0 and 3.0 during the previous 6 months of clinic visits were included. All patients were anticoagulated with acenocoumarol. Patients with prosthetic heart valves, acute coronary syndrome, stroke (ischemic or embolic), valvular AF, or any hemodynamic instability, as well as patients who had been admitted to hospital or had surgical intervention in the preceding 6 months, were excluded from the study. A history of malignancy was allowed if the patient's expected survival duration was $>$ 6 months and the patient was not receiving chemotherapy or radiotherapy at study entry. A complete medical history was recorded. Follow-up was performed through visits to the anticoagulation clinic.

The HAS-BLED bleeding risk score was calculated as a measure of baseline bleeding risk, as the result of adding one point for hypertension, abnormal renal/liver function (one point each), stroke, bleeding history or predisposition, labile INR, elderly (\geq 65 years), and drugs (eg, concomitant aspirin or nonsteroidal antiinflammatory drugs)/alcohol abuse (one point for each one factor, maximum HAS-BLED score = 9). Based on our inclusion criteria at entry, labile INR was quantified as zero in every patient. The ATRIA score is the result of adding three points for anemia or severe renal disease, two points for age \geq 75 years, and one point each for prior hemorrhage and diagnosed hypertension.

We assessed both bleeding risk scores as quantitative variables or as a dichotomized variable (low-moderate vs high risk). As per their original definitions, a high risk of bleeding was considered with a HAS-BLED score of at least three points or an ATRIA score of at least five points.

During follow-up, bleeding events were assessed by the 2005 International Society on Thrombosis and Haemostasis criteria.¹³ The definitions were as follows: fatal bleeding; and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome; and/or bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or RBCs.

This was a single-center cohort study, and, thus, bleeding events were recorded using standardized criteria, as mentioned previously.¹³ Follow-up information was carefully obtained from patient visits at the anticoagulation clinic or via the hospital electronic medical records system, or, when those sources were unavailable, by telephone interview.

The protocol study was approved by the Ethics Committee for Clinical Investigation (reference 09/08; June 26, 2008) of the Hospital Universitario Morales Meseguer, Murcia, and all patients gave informed consent to participation in the study. The ethics approval was given to study the data set of patients who were initially entered into our anticoagulation clinic database in

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2007, to allow the long-term follow-up of this cohort for adverse events (eg, thromboembolism, bleeding, and so forth) and their clinical predictors. The various clinical parameters needed to calculate the HAS-BLED and ATRIA scores (described in 2010 and 2011, respectively) were available on our database, and, thus, the scores were applied retrospectively to the cohort for the present analysis.

Statistical Analysis

Continuous variables were tested for normality by the Kolmogorov-Smirnov test. Continuous variables are presented as mean \pm SD or median (interquartile range [IQR]), as appropriate, and categorical variables as a percentage. Cox models were used to determine the associations between both risk scores and bleeding. To contrast prognostic accuracy, statistical comparison of receiver-operating characteristic curves was performed.

Model performance was evaluated by calculating C statistics, and the improvement in predictive accuracy was evaluated by calculating the net reclassification improvement (NRI) and integrated discrimination improvement (IDI), as described by Pencina et al,¹⁴ where the categories of probability for events are defined based on the HAS-BLED or ATRIA bleeding risk scores. We compared the risk scales using two different approaches: (1) a quantitative model comparison and (2) a dichotomized model comparison (ie, low-moderate and high bleeding risk). $P < .05$ was accepted as statistically significant. Statistical analyses were performed using SPSS 15.0 for Windows (IBM) and SAS software (version 9.2; SAS Institute Inc).

RESULTS

We included 937 patients (49% men; median age, 76 years; IQR, 70-81 years) (Table 1). The median CHADS₂ (congestive heart failure, hypertension, age \geq 75 years, diabetes mellitus, and prior stroke or transient ischemic attack) risk score was 2 (IQR, 2-3), and 76% of patients had a CHADS₂ risk score \geq 2. The median CHA₂DS₂-VASc (cardiac failure or dysfunction, hypertension, age \geq 75 years [doubled], diabetes, stroke [doubled], vascular disease, age 65-74 years, sex [female] category) score was 4 (3-5), and 93% had a CHA₂DS₂-VASc score \geq 2. The median HAS-BLED score was 2 (2-3), and 35% of patients had a HAS-BLED score \geq 3. The median ATRIA score was 3 (1-3), and 16% had an ATRIA score \geq 5.

Median follow-up was 952 (785-1,074) days. During this period, 79 patients (3.2%/y) presented with a hemorrhagic event; of these, 16 were intracranial hemorrhages (0.6%/y). Ninety-three patients (3.8%/y) died during the follow-up, and, of these deaths, seven (0.3%/y) were as a result of a hemorrhagic event. Using an unadjusted (crude) analysis, the HAS-BLED score was predictive for major bleeding events, as a continuous variable (per point; hazard ratio [HR], 2.23 [1.82-2.73]; $P < .001$) and a HAS-BLED score \geq 3 had an HR of 4.55 (2.82-7.33; $P < .001$). The ATRIA score was also predictive for major bleeding events (per point; HR, 1.34 (1.22-1.48); $P < .001$), and an

Table 1—Baseline Clinical Characteristics of Patients With AF

Baseline Characteristics	Patients With AF (N = 937)
Male sex	461 (49)
Age, y	76 (70-81)
Age \geq 75 y	539 (57)
Hypertension	773 (82)
Diabetes mellitus	239 (25)
Heart failure	346 (37)
History of stroke or TIA	176 (19)
Renal impairment	91 (10)
Coronary artery disease	179 (19)
Current alcoholic consumption	27 (3)
Previous bleeding episode	84 (9)
Antiplatelet therapy	162 (17)
HAS-BLED score	2 (2-3)
0	23 (2.4)
1	139 (15)
2	450 (48)
3	215 (22.9)
4	89 (9.4)
5	18 (2)
6	3 (0.3)
ATRIA score	3 (1-3)
0	70 (7.5)
1	254 (27)
3	63 (7)
4	321 (34)
5	80 (8.5)
6	24 (3)
7	93 (10)
8	17 (2)
9	3 (0.3)
12	12 (1.3)
CHADS ₂ score	2 (2-3)
CHADS ₂ \geq 2	713 (76)

Data are presented as No. (%) or median (interquartile range). AF = atrial fibrillation; ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; CHADS₂ = congestive heart failure, hypertension, age \geq 75 years, diabetes mellitus, and prior stroke or transient ischemic attack; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly; TIA = transient ischemic attack.

ATRIA score \geq 5 had an HR of 3.05 (1.87-4.68, $P < .001$). The incidence of major bleeding events according to each point on the HAS-BLED or ATRIA scores is shown in Figure 1.

For intracranial hemorrhage, the HAS-BLED score as a continuous variable had an HR of 2.58 (1.65-4.02, $P < .001$), whereas the HR for the ATRIA score did not reach statistical significance (HR, 1.18 [0.94-1.50]; $P = .159$). The HAS-BLED score, as a dichotomized variable (\geq three points), was associated with intracranial hemorrhage (HR, 4.89 [1.69-14.14]; $P = .003$). An ATRIA score \geq 5 was not significantly associated with intracranial hemorrhage (HR, 0.95 [0.21-4.17]; $P = .941$).

As detailed in Table 2, the HAS-BLED score showed a model performance (based on C statistics)

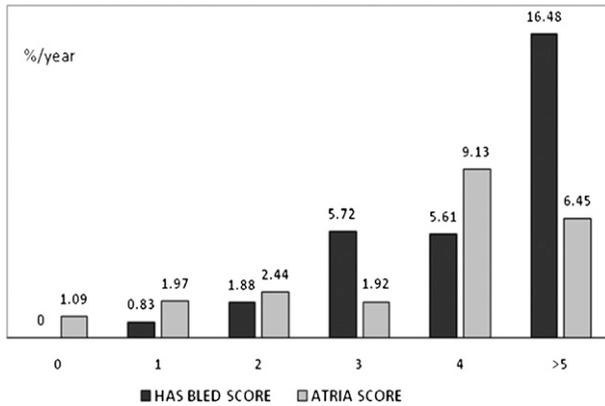


FIGURE 1. Incidence (%/y) of major bleeding events according to the HAS-BLED and ATRIA scores. ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly.

similar to that of the ATRIA score as a quantitative variable (C statistic, 0.71 vs 0.68; $P = .356$) but was superior to the ATRIA score when analyzed as a dichotomized variable (C statistic, 0.68 vs 0.59; $P = .035$).

Both NRI and IDI analyses show how the HAS-BLED score predicted major bleeding episodes more accurately than did the ATRIA risk score. Based on reclassification analyses, the NRIs were 13.6% ($P = .043$) for the quantitative model and 19.6% ($P = .019$) for the dichotomized model, whereas the IDIs were 6.9% and 7.0% ($P = .033$ and $P = .001$, respectively). The probability of correctly predicting serious bleeding events using the HAS-BLED score was particularly reflected in the percentage of events correctly reclassified.

DISCUSSION

In this study, we show, to our knowledge for the first time, that the HAS-BLED score has a signifi-

cantly better prediction accuracy than the weighted (and slightly more complex) ATRIA score, when applied in a quantitative or dichotomized manner (as in current guidelines). Our novel findings extend the findings of previous studies⁷⁻¹¹ and also reinforce the incremental usefulness of the simple HAS-BLED score over other published bleeding risk scores in patients with AF.

The HAS-BLED bleeding score is a simple and useful tool that can be applied in daily practice. Since its first description in 2010 by Pisters et al,⁷ this score has been validated in several populations and has been shown to outperform several older (and more complicated) bleeding risk scores.⁸⁻¹¹ In an analysis of an unselected nationwide cohort of hospitalized patients with AF, for example, the simple HAS-BLED score was comparable to the (more complex) HEMORR₂HAGES (hepatic or renal disease, ethanol use, malignancy, reduced platelet count, rebleeding, hypertension, anemia, genetic factors, elevated risk of fall including neuropsychiatric disease, stroke) in predicting bleeding risk.⁹ In a separate analysis published > 1 year after the first HAS-BLED publication, the ATRIA score was compared with and performed better than several older bleeding risk scores, including HEMORR₂HAGES,¹² but the HAS-BLED score was not compared in that analysis.¹⁵ Indeed, to our knowledge, there has never been a prior published (or presented) study that directly compares the HAS-BLED and ATRIA scores.

In the present analysis of “real-world,” chronic, stable, patients with AF receiving anticoagulant therapy, the HAS-BLED score had a better model performance than did the ATRIA score when applied as a dichotomized or quantitative variable. The probability of correctly predicting serious bleeding events using the HAS-BLED score was particularly reflected in the percentage of events correctly reclassified.

Stroke risk is closely related to bleeding risk in patients with AF.^{16,17} Indeed, many risk factors for thromboembolism, such as advanced age, uncontrolled

Table 2—Evaluating Predictive Ability of the HAS-BLED Score vs ATRIA Score for Detection of Major Bleeding Using C Statistics, Relative NRI, and IDI Indexes

Models	C Statistic		Relative			% Events Correctly			% No. Events Correctly Reclassified
	(95% CI)	P Value	IDI, %	P Value	NRI	SD	P Value	Reclassified Using HAS-BLED Compared With ATRIA	
Quantitative model									
ATRIA (quantitative)	0.68 (0.65-0.71)
HAS-BLED (quantitative)	0.71 (0.68-0.74)	.356 ^a	6.9	.033 ^a	0.136	0.067	.043 ^a	8.86	4.78
Dichotomized model									
ATRIA (0-4 vs ≥ 5)	0.59 (0.55-0.62)
HAS-BLED (0-2 vs ≥ 3)	0.68 (0.65-0.71)	.035 ^b	7.0	.001 ^b	0.196	0.083	.019 ^b	36.71	-17.13

IDI = integrated discrimination improvement; NRI = net reclassification improvement. See Table 1 for expansion of other abbreviations.

^aFor quantitative models comparison.

^bFor dichotomized models comparison.

hypertension, history of ischemic heart disease, cerebrovascular disease, or previous bleeding events, have also been identified as risk factors for bleeding.⁴ In clinical practice, an estimation of both stroke and bleeding risks is essential to guide the selection of the most appropriate thromboprophylaxis.^{5,6} We have recently demonstrated that the HAS-BLED score was a good predictor of major bleeding risk (performing as well as a multivariate model) but was only modestly predictive for cardiovascular events or mortality (and did not compare well with a multivariate model).¹⁰ Thus, the HAS-BLED score was a better predictor of major bleeding than of thrombotic events in patients with AF.

It is worth emphasizing that the HAS-BLED score was designed not only to make physicians stop prescribing OAC in those with high HAS-BLED scores, but also to identify patients who have to be more carefully managed and/or reviewed, or to highlight the common correctable bleeding risk factors that can be addressed, such as uncontrolled BP (the “H” in HAS-BLED), labile INRs (the “L” in HAS-BLED), or concomitant aspirin use (the “D” in HAS-BLED).¹⁸ Our findings support recommendations in current international guidelines for exercising caution and/or regular review in patients with a HAS-BLED score ≥ 3 , but HAS-BLED can help identify modifiable bleeding risks (eg, uncontrolled BP), which need to be addressed.^{5,19} Importantly, a high HAS-BLED score per se should not, on its own, be used to exclude patients from OAC therapy.¹⁹ Despite the bleeding risk with high HAS-BLED scores, the net clinical benefit of balancing ischemic stroke against serious bleeding still leans in favor of OAC use, given that these patients would be at increased risk of stroke/thromboembolism.²⁰

Limitations

The strength of our study is its inclusion of consecutive patients attending our anticoagulation clinic, with careful follow-up. However, we included only stable, warfarin-experienced patients, whereas naive or unstable patients were excluded. Thus, there could be a selection bias, especially because the risk of bleeding on anticoagulant therapy or of having a thromboembolic event is highest during the period immediately after coumarins are initiated.²¹ Nonetheless, we wished to avoid confounding factors regarding the occurrence of adverse events, so they could not be attributable to poor INR control or other residual confounding. Secondly, we wanted to homogenize the study population at study entry. Finally, we did not perform adjudication of bleeding events because this was a single-center cohort study (not a clinical trial), but all events were defined according

to standardized criteria, as recommended by the International Society on Thrombosis and Haemostasis (see the “Materials and Methods” section).

CONCLUSIONS

In patients with AF receiving anticoagulant therapy, the HAS-BLED score shows significantly better prediction ability than the weighted (and slightly more complex) ATRIA score. Our findings reinforce the incremental usefulness of the HAS-BLED score over other bleeding risk scores in patients with AF.

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Dr Fernández: contributed to the data analyses and drafting and revisions of the final article.

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Dr Vicente: contributed to the data analyses and drafting and revisions of the final article.

Dr Lip: contributed to the idea and hypothesis of the study, supervision of the analyses, and drafting and revisions of the final article.

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